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Published in:
Clinical Journal of the American Society of Nephrology

DOI:
10.2215/CJN.06600521

Airflow Limitation, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients

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Abstract

Background and objectives Many kidney transplant recipients suffer from fatigue and poor health-related quality of life. Airflow limitation may be an underappreciated comorbidity among kidney transplant recipients, which could contribute to fatigue and lower health-related quality of life in this population. In this study, we compared the prevalence of airflow limitation between kidney transplant recipients and healthy controls and investigated associations of airflow limitation with fatigue and health-related quality of life in kidney transplant recipients.

Design, setting, participants, & measurements Data from the ongoing TransplantLines Biobank and Cohort study were used. Airflow limitation was defined as forced exhaled volume in 1 second less than the fifth percentile of the general population. Fatigue and health-related quality of life were assessed using checklist individual strength 20 revised (CIS20-R) and Short Form-36 (SF-36) questionnaires.

Results A total of 539 kidney transplant recipients (58% men; mean age 56±13 years) and 244 healthy controls (45% men; mean age 57±10 years) were included. Prevalence of airflow limitation was higher in kidney transplant recipients than in healthy controls (133 [25%] versus 25 [10%]). In multinomial regression models, airflow limitation was independently associated with fatigue severity (odds ratio moderate fatigue, 1.68; 95% confidence interval, 0.92 to 3.09 and odds ratio severe fatigue, 2.51; 95% confidence interval, 1.39 to 4.55; $P=0.007$) and lower physical health-related quality of life (−0.11 SDs; 95% confidence interval, −0.19 to −0.02; $P=0.01$) in kidney transplant recipients. In exploratory mediation analyses, fatigue accounted for 79% of the association of airflow limitation with physical health-related quality of life.

Conclusions Airflow limitation is common among kidney transplant recipients. Its occurrence is associated with more than two times higher risk of severe fatigue, and it is associated with lower physical health-related quality of life. Mediation analyses suggest that airflow limitation causes fatigue, which in turn, decreases physical health-related quality of life.

Clinical Trial registry name and registration number: TransplantLines: The Transplantation Biobank, NCT03272841

CJASN 16: 1686–1694, 2021. doi: https://doi.org/10.2215/CJN.06600521

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Introduction

Kidney transplant recipients frequently suffer from fatigue and have lower health-related quality of life (HRQoL) compared with the general population (1,2). The health status and reported HRQoL of kidney transplant recipients after successful transplantation depend largely on individual patient characteristics and comorbidities, rather than graft function alone (3). Consequently, underlying comorbidities are increasingly recognized as key targets to reduce fatigue and improve HRQoL among kidney transplant recipients. We propose that airflow limitation is an important, hitherto overlooked, comorbidity after kidney transplantation.

It is well established that airflow limitation is associated with fatigue and poor HRQoL in patients with chronic obstructive pulmonary disease (COPD) (4,5). It is also known that airflow limitation is prevalent in patients with other chronic diseases, including diabetes, heart failure, and CKD (6–10). Whether kidney transplant recipients are at higher risk of airflow limitation and whether its occurrence is associated with fatigue and lower HRQoL have remained unexplored in this population to date. Importantly, airflow limitation can be treated and may, therefore, serve as a therapeutic target to improve fatigue and HRQoL among kidney transplant recipients (11–14).

Among stable kidney transplant recipients, we aimed to assess the prevalence of airflow limitation in comparison with healthy controls and to identify potential clinical and biochemical determinants of

airflow limitation. In addition, we investigated the association of prevalent airflow limitation with HRQoL and whether this association may be mediated by fatigue to gain insight into the potential causal pathway between airflow limitation and lower HRQoL in kidney transplant recipients.

Materials and Methods

Study Population

We used data from the ongoing, prospective TransplantLines Biobank and Cohort study (ClinicalTrials.gov identifier NCT03272841). From June 2015, all patients with solid organ transplants and donors (aged ≥18 years) of the University Medical Center Groningen (UMCG; The Netherlands) were invited to participate. All participants gave written informed consent on enrollment. The study protocol was approved by the local institutional review board (METc 2014/077), adheres to the UMCG Biobank Regulation, and is in accordance with the WMA Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (15). We selected stable kidney transplant recipients with a functional graft for ≥1 year after transplantation with available data on airflow limitation and HRQoL (n=539). We also included potential living kidney donors (n=244) as healthy controls. A consort flow diagram is shown in Supplemental Figure 1. Kidney transplant recipients in the study sample did not differ materially from the remaining patients in the parent cohort (Supplemental Table 1). All study procedures were performed between June 2015 and February 2020.

Assessment of Airflow Limitation

The degree of airflow limitation was measured using forced exhaled volume in 1 second (FEV_1) with an Asma-1 handheld spirometer (Vitalograph, Buckingham, United Kingdom) (16). Participants were instructed to breathe in maximally without the spirometer and to breathe out maximally and as fast as possible into the spirometer in a standing position. FEV_1 measurements were performed thrice per study subject, where the highest value was used (15,17). The highest FEV_1 measurements that were used in further analyses were very strongly correlated with the second highest FEV_1 measurements (Pearson correlation coefficient =0.98), indicating robust reliability of this measurement. The predicted FEV_1 was then calculated using the GLI-2012 equation (18). The percentage of predicted FEV_1 was calculated as (FEV_1/predicted FEV_1)×100%. Airflow limitation was defined as FEV_1 less than the fifth percentile (z score <-1.64) of an age-, sex-, height-, and ethnicity-matched population on the basis of data from 74,187 individuals (18).

Assessment of Fatigue and Health-Related Quality of Life

Fatigue was assessed using the checklist individual strength 20 revised (CIS20-R), where the subscore of fatigue severity was used (19). Moderate and severe fatigue were defined as scores ≥20 and ≥35, respectively (20,21). To assess HRQoL, a Dutch translation of the Short Form-36 Health Survey was used. The physical component scale (PCS) was calculated using the mean score on general health, physical health, role limitations due to impairment of physical health, and pain items. The mental component scale (MCS) was calculated by averaging the scores for emotional well-being, role limitations due to emotional problems, impaired social functioning, and impaired vitality (22,23). Higher PCS and MCS scores indicate better perceived HRQoL (24).

Definitions

The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation (25). Diabetes mellitus was defined as hemoglobin A1c ≥7%, a nonfasting blood glucose ≥200 mg/dl, a fasting blood glucose ≥126 mg/dl, and/or use of antidiabetic drugs. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, and/or use of antihypertensive medication. Information regarding other comorbidities, including COPD, bronchial asthma, heart failure, and sleep apnea syndrome, was extracted from the patient records.

Statistical Analyses

Data distribution was visually assessed using histograms and Q–Q plots. Normally distributed variables are presented as mean ± SD, non-normally distributed variables are presented as medians (interquartile ranges), and categorical variables are presented as n (valid percentages).

We used binary logistic regression analyses to assess associations of clinical and biochemical parameters with airflow limitation. Additionally, we performed multivariable logistic regression analyses adjusted for age and adjusted for age and sex. We used multinomial logistic regression analyses to investigate associations between airflow limitation and fatigue severity. Linear regression analyses were used to assess associations of airflow limitation with PCS and MCS. Regression coefficients were provided as standardized β-coefficients (st. β-coefficients), referring to the number of SDs as dependent variable changes per SD higher value of the independent variable, with 95% confidence intervals (95% CIs). In mentioned regression analyses, we cumulatively adjusted for potential confounders, including age, sex, body mass index (model 1), diabetes, dialysis, $\log_2$ N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (model 2), smoking history, mammalian target of rapamycin inhibitor use, sleep apnea syndrome, and COPD (model 3). No adjustment for inhalation medication use was performed because of collinearity with COPD. Regression analyses were performed using pairwise exclusion. We performed mediation analyses (26) as described by Preacher and Hayes (27) using bootstrapping procedures with adjustment for variables present in model 3 using the R package "mediation." The mediated proportion is the ratio of the total effect to the natural indirect effect. It thereby provides an estimate of the extent to which the total effect is accounted for by the pathway through the mediating variable. A large mediated proportion indicates that the total effect of the exposure on the outcome is through the mediating variable.

Statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY) with the exception of

the mediation analyses, which were performed using R version 3.5.1 (Vienna, Austria). Log_2 or square root transformations were performed if necessary to meet the assumptions for regression analyses. To adjust for multiple testing, a P value=0.02 denoted statistical significance in regression analyses (according to the Bonferroni method because we assessed the following three hypotheses: [*1*] airflow limitation is associated with fatigue, [*2*] airflow limitation is associated with mental HRQoL, and [*3*] airflow limitation is associated with physical HRQoL).

Sensitivity Analyses

To further test for robustness of found associations, we repeated the regression analyses with fatigue and physical HRQoL using a cutoff value of <2.5th percentile (z score <-1.96) of the general population to define airflow limitation. Additionally, we repeated these analyses with FEV_1 as a continuous variable, with additional adjustment for height, as a generally accepted determinant of FEV_1 (18).

Results

Baseline Characteristics

We included 539 kidney transplant recipients (58% men; mean age 56±13 years) and 244 healthy controls (45% men; mean age 57±10 years). Among kidney transplant recipients, median time since transplantation was 8 (3–13) years, and 270 (50%) underwent dialysis before transplantation. Diabetes and hypertension were prevalent among kidney transplant recipients (27% and 88%, respectively). Prevalence of airflow limitation was higher in kidney transplant recipients compared with healthy controls (133 [25%] versus 25 [10%], respectively). FEV_1 of kidney transplant recipients was lower than FEV_1 of healthy controls both in men and in women (men: 3.21±0.76 versus 3.54±0.66 L; women: 2.37±0.55 versus 2.73±0.54 L). Percentage of predicted FEV_1 was also lower in kidney transplant recipients compared with healthy controls (86%±16% versus 98%±18%). More detailed baseline characteristics are shown in Table 1.

Comorbidities among Kidney Transplant Recipients with Airflow Limitation

Prevalence rates of diabetes, sleep apnea syndrome, and COPD were higher among kidney transplant recipients with airflow limitation compared with recipients without airflow limitation (35% versus 24%, 7% versus 2%, and 8% versus 3%, respectively). Among recipients with airflow limitation, 86% had hypertension, 8% had congestive heart failure, and 5% had bronchial asthma. Prevalence rates of these comorbidities were comparable with prevalence rates in recipients without airflow limitation.

Analyses with Airflow Limitation as the Dependent Variable

In univariable logistic regression analyses with airflow limitation as the dependent variable in kidney transplant recipients, age was inversely associated with risk of having airflow limitation (odds ratio [OR] per 10-year increment, 0.75; 95% CI, 0.65 to 0.88). No association with sex was found. In bivariable analyses adjusted for age, dialysis before transplantation (OR, 1.72; 95% CI, 1.14 to 2.59), diabetes (OR, 2.28; 95% CI, 1.36 to 3.84), sleep apnea syndrome (OR, 4.16; 95% CI, 1.55 to 11.14), COPD (OR, 4.02; 95% CI, 1.66 to 9.70), NT-proBNP (OR per doubling, 1.22; 95% CI, 1.09 to 1.36), mammalian target of rapamycin use (OR, 2.66; 95% CI, 1.06 to 6.65), bronchodilator use (OR, 3.52; 95% CI, 1.65 to 7.55), and inhalation steroid use (OR, 3.60; 95% CI, 1.62 to 8.02) were associated with airflow limitation. After additional adjustment for sex, point estimates of these associations changed slightly, as shown in Table 2.

Association of Airflow Limitation with Fatigue

Prevalence of moderate fatigue was approximately two times higher in kidney transplant recipients compared with healthy controls (179 [33%] versus 44 [18%]), and prevalence of severe fatigue was approximately seven times higher in kidney transplant recipients compared with healthy controls (194 [36%] versus 13 [5%]), as shown in Supplemental Table 2. Recipients with moderate and severe fatigue had airflow limitation more frequently compared with recipients with no to mild fatigue (30% and 50% versus 20%, respectively). Univariable multinomial analysis indicated a significant association of airflow limitation with fatigue severity (OR moderate fatigue, 1.35; 95% CI, 0.78 to 2.34 and OR severe fatigue, 2.44; 95% CI, 1.46 to 4.09; P=0.001), which remained materially unchanged after adjustment for potential confounders, as shown in Table 3.

Associations of Airflow Limitation with Health-Related Quality of Life

Both PCS and MCS scores of HRQoL were lower among kidney transplant recipients compared with healthy controls (PCS: 67.2±22.5 versus 90.1±10.5; MCS: 76.2±17.4 versus 88.2±11.1) (Supplemental Table 2). Univariable linear regression analyses showed that airflow limitation was associated with lower HRQoL in kidney transplant recipients (PCS: difference expressed as st. $\beta=-0.13$; 95% CI, −0.21 to −0.04; P=0.004 and MCS: difference expressed as st. $\beta=-0.11$; 95% CI, −0.19 to −0.02; P=0.01). The association with mental HRQoL lost significance after adjustment for potential confounders, whereas the association with physical HRQoL remained statistically significant, as shown in Table 4.

Mediation Analyses

Fatigue strongly mediated the effect of airflow limitation on physical HRQoL (proportion mediated: 79%), independent of adjustment for potential confounders (Supplemental Table 3). The causal path suggested by these analyses is shown in Figure 1.

Sensitivity Analyses

Associations of airflow limitation as defined using the alternative cutoff value for airflow limitation (<2.5th percentile) with fatigue severity and physical HRQoL were even stronger than in primary analyses (Supplemental Tables 4 and 5). Additionally, sensitivity analyses with FEV_1 as the continuous variable, presented in Supplemental Tables 6 and 7, also showed a stronger association with physical HRQoL compared with the primary analyses using a cutoff for airflow limitation (PCS: difference expressed as st. $\beta=0.28$; 95% CI, 0.20 to 0.36; $P<0.001$).

Table 1. Baseline characteristics of participants in the TransplantLines Biobank and Cohort study who have received a kidney transplant and healthy controls

Baseline Variables	Kidney Transplant Recipients	Healthy Controls
Study participants, *n* (%)	539	244
Pulmonary assessment		
Airflow limitation, *n* (%)	133 (25)	25 (10)
Percentage of predicted FEV_1, %	86.4±16.0	97.5±18.4
FEV_1, L		
FEV_1 of men	3.21±0.76	3.54±0.66
FEV_1 of women	2.37±0.55	2.73±0.54
Characteristics		
Men, *n* (%)	310 (58)	110 (45)
Age, yr	56±13	57±10
Height, cm	173±9	174±10
Weight, kg	81±17	82±28
Body mass index, kg/m^2	27±5	27±8
Primary kidney disease, *n* (%)		
Unknown	125 (23)	n/a
Inflammatory disease	171 (32)	n/a
Congenital and hereditary kidney disease	146 (27)	n/a
Kidney vascular disease, excluding vasculitis	26 (5)	n/a
Diabetic kidney disease	21 (4)	n/a
Other	50 (9)	n/a
Dialysis before transplantation, *n* (%)	270 (50)	n/a
If yes, time on dialysis, yr	3 (2–5)	n/a
Time since transplantation, yr	8 (3–13)	n/a
Hypertension, *n* (%)	477 (88)	65 (27)
Diabetes, *n* (%)	143 (27)	2 (0.8)
Sleep apnea syndrome, *n* (%)	17 (3)	1 (0.4)
Congestive heart failure, *n* (%)	27 (5)	1 (0.4)
Bronchial asthma, *n* (%)	15 (3)	8 (3)
Chronic obstructive pulmonary disease, *n* (%)	22 (4)	3 (1)
History of smoking, *n* (%)		
Never	286 (53)	112 (46)
<20 yr	108 (20)	46 (19)
>20 yr	145 (27)	86 (35)
Laboratory measurements		
C-reactive protein, mg/L	1.7 [0.7–4.7]	1.1 [0.6–2.4]
Albumin, g/dl	4.3±0.3	4.5±0.2
NT-proBNP, pg/ml	227 [96–519]	56 [32–105]
eGFR, ml/min per 1.73 m^2	50±18	78±17
Medication, *n* (%)		
Prednisolone	518 (96)	0 (0)
Calcineurin inhibitor	296 (55)	0 (0)
Proliferation inhibitors		
Azathioprine	70 (13)	0 (0)
Mycophenolic acid	374 (69)	0 (0)
mTOR inhibitor	20 (4)	0 (0)
Bronchodilator drugs	31 (5)	6 (2)
Inhalation steroids	27 (5)	10 (4)

Normally distributed data are presented as means ± SDs, non-normally distributed data are presented as medians [interquartile ranges], and categorical data are presented as numbers (valid percentages). Data regarding C-reactive protein, albumin, and NT-proBNP were missing in four (1%), one (0.2%), and 14 (3%), respectively, of the kidney transplant recipients. Data regarding C-reactive protein, albumin, NT-proBNP, and eGFR were missing in 30 (12%), 24 (10%), 39 (16%), and 24 (10%), respectively, of the healthy controls. Other variables had no missing data. FEV_1, forced exhaled volume in 1 second; n/a, not applicable; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; mTOR, mammalian target of rapamycin.

Discussion

We found that one in four kidney transplant recipients had airflow limitation, which is more than twice the prevalence in the healthy controls group. Notably, diabetes, sleep apnea syndrome, COPD, higher NT-proBNP, and dialysis before transplantation were independently associated with a higher risk of airflow limitation in kidney transplant recipients. Airflow limitation more than doubles the risk of experiencing severe fatigue, and it is associated with lower physical HRQoL in kidney transplant recipients. The association with physical HRQoL was strongly mediated by fatigue. This is the first study to show that airflow limitation is highly prevalent among kidney transplant recipients and that it is associated with fatigue severity and lower physical HRQoL.

Although no previous studies have investigated the prevalence of airflow limitation among kidney transplant recipients, several small studies assessed FEV_1 in kidney transplant

Table 2. Characteristics associated with airflow limitation among kidney transplant recipients

Variable	Airflow Limitation, *n* (%)	Difference (95% Confidence Interval)		
		Univariable	Adjusted for Age	Adjusted for Age and Sex
Characteristics				
Sex				
Women	48 (21)	1 (reference)	1	n/a
Men	85 (27)	1.43 (0.95 to 2.13)	1.46 (0.97 to 2.21)	—
Age, per 10 yr		0.75 (0.65 to 0.88)	—	—
Height, per 10 cm		1.07 (0.87 to 1.33)	0.84 (0.63 to 1.12)	0.84 (0.62 to 1.12)
Weight, per 10 kg		1.12 (0.99 to 1.25)	1.11 (0.99 to 1.25)	1.08 (0.96 to 1.23)
Body mass index, kg/m^2		1.04 (1.00 to 1.08)	1.04 (1.00 to 1.08)	1.04 (1.00 to 1.09)
Dialysis before transplantation				
No	56 (21)	1 (reference)	1 (reference)	1 (reference)
Yes	77 (29)	1.52 (1.02 to 2.25)	1.72 (1.14 to 2.59)	1.72 (1.14 to 2.59)
If yes, sqrt time on dialysis, per yr		1.37 (0.90 to 2.08)	1.40 (0.92 to 2.14)	1.43 (0.94 to 2.19)
Time since transplantation, per doubling		0.98 (0.85 to 1.12)	0.99 (0.86 to 1.15)	0.99 (0.86 to 1.14)
Hypertension				
No	19 (31)	1 (reference)	1 (reference)	1 (reference)
Yes	114 (24)	0.71 (0.40 to 1.27)	0.84 (0.46 to 1.53)	0.77 (0.42 to 1.41)
Diabetes				
No	86 (22)	1 (reference)	1 (reference)	1 (reference)
Yes	47 (33)	1.77 (1.16 to 2.7)	2.28 (1.36 to 3.84)	2.29 (1.36 to 3.86)
Sleep apnea syndrome				
No	124 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	9 (53)	3.61 (1.36 to 9.56)	4.16 (1.55 to 11.14)	3.73 (1.38 to 10.10)
Congestive heart failure				
No	123 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	10 (37)	1.86 (0.83 to 4.17)	2.18 (0.96 to 4.96)	2.22 (0.97 to 5.06)
Bronchial asthma				
No	127 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	6 (40)	2.08 (0.73 to 5.97)	2.13 (0.73 to 6.22)	2.08 (0.71 to 6.07)
Chronic obstructive pulmonary disease				
No	122 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	11 (50)	3.24 (1.37 to 7.65)	4.02 (1.66 to 9.70)	3.91 (1.61 to 9.47)
History of smoking				
Never	72 (25)	1 (reference)	1 (reference)	1 (reference)
<20 yr	22 (20)	0.76 (0.44 to 1.30)	0.86 (0.49 to 1.49)	0.87 (0.50 to 1.52)
>20 yr	39 (27)	1.08 (0.69 to 1.70)	1.43 (0.88 to 2.31)	1.43 (0.88 to 2.32)
Laboratory measurements				
C-reactive protein, mg/L, per doubling		1.07 (0.96 to 1.19)	1.10 (0.99 to 1.22)	1.10 (0.99 to 1.22)
Albumin, per g/dl		1.01 (0.53 to 1.94)	0.64 (0.32 to 1. 72)	0.63 (0.32 to 1.26)
NT-proBNP, pg/ml, per doubling		1.09 (0.99 to 1.21)	1.22 (1.09 to 1.36)	1.24 (1.11 to 1.39)
eGFR, per 10 ml/min per 1.73 m^2		1.02 (0.91 to 1.14)	1.00 (0.90 to 1.12)	1.00 (0.89 to 1.12)
Medication				
Prednisolone				
No	5 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	128 (25)	1.05 (0.38 to 2.92)	1.20 (0.42 to 3.40)	1.15 (0.41 to 3.26)
Calcineurin inhibitor				
No	37 (27)	1 (reference)	1 (reference)	1 (reference)
Yes	96 (24)	0.84 (0.54 to 1.30)	0.77 (0.49 to 1.21)	0.78 (0.50 to 1.23)
Proliferation inhibitors				
Azathioprine				
No	112 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	21 (30)	1.37 (0.79 to 2.38)	1.38 (0.79 to 2.43)	1.39 (0.79 to 2.45)
Mycophenolic acid				
No	45 (27)	1 (reference)	1 (reference)	1 (reference)
Yes	88 (24)	0.82 (0.54 to 1.25)	0.82 (0.53 to 1.25)	0.79 (0.51 to 1.21)
mTOR inhibitor				
No	124 (24)	1 (reference)	1 (reference)	1 (reference)
Yes	9 (45)	2.61 (1.06 to 6.44)	2.66 (1.06 to 6.65)	2.71 (1.08 to 6.78)
Bronchodilator drugs				
No	119 (23)	1 (reference)	1 (reference)	1 (reference)
Yes	14 (45)	2.69 (1.29 to 5.62)	3.52 (1.65 to 7.55)	3.56 (1.66 to 7.63)
Inhalation steroids				
No	120 (23)	1 (reference)	1 (reference)	1 (reference)
Yes	13 (48)	3.03 (1.39 to 6.63)	3.60 (1.62 to 8.02)	3.63 (1.63 to 8.07)

Assessed variables were associated with an *x*-higher risk of airflow limitation, with differences representing odds ratios and their 95% confidence intervals. Data regarding C-reactive protein, albumin, and NT-proBNP were missing in four (1%), one (0.2%), and 14 (3%), respectively, of the kidney transplant recipients. Other variables had no missing data. n/a, not applicable; sqrt, square root; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; mTOR, mammalian target of rapamycin.

Table 3. Associations of airflow limitation with fatigue among kidney transplant recipients

		Fatigue Severity			
Variable	*N*	No or Mild Fatigue Odds Ratio (95% Confidence Interval)	Moderate Fatigue Odds Ratio (95% Confidence Interval)	Severe Fatigue Odds Ratio (95% Confidence Interval)	*P* Value
CIS20R severity score		<20	20–34	≥35	
Airflow limitation, *n* (%)		26 (20)	39 (30)	65 (50)	
Crude	525	1 (reference)	1.35 (0.78 to 2.34)	2.44 (1.46 to 4.09)	0.001
Model 1	525	1 (reference)	1.56 (0.88 to 2.75)	2.84 (1.65 to 4.91)	<0.001
Model 2	511	1 (reference)	1.62 (0.89 to 2.94)	2.59 (1.45 to 4.62)	0.005
Model 3	511	1 (reference)	1.68 (0.92 to 3.09)	2.51 (1.39 to 4.55)	0.007

Results of multinomial logistic regression analyses with the fatigue category as the dependent variable are shown. Airflow limitation was associated with an *x*-higher risk of moderate or severe fatigue, with differences representing odds ratios and their 95% confidence intervals. Model 1 was adjusted for sex, age, and body mass index. Model 2 was model 1 additionally adjusted for diabetes, dialysis before transplantation, and $\log_2$ N-terminal prohormone of brain natriuretic peptide. Model 3 was model 2 additionally adjusted for history of smoking, mammalian target of rapamycin inhibitor use, sleep apnea syndrome, and chronic obstructive pulmonary disease. CIS20R, checklist individual-strength 20 revised.

recipients. The mean percentage of predicted FEV_1 among kidney transplant recipients in our study was 86%, which is similar to other studies that reported percentages of 90% in 24 kidney transplant recipients and 90% in 20 kidney transplant recipients with type 1 diabetes mellitus (28,29). Slight differences might be explained by different measurement protocols and different population characteristics. Our study population was much larger, and we applied no specific inclusion or exclusion criteria with regard to age, sex, or comorbidities, which suggests that the FEV_1 found in our study likely is representative of FEV_1 in the outpatient kidney transplant recipients population at large.

A lower percentage of predicted FEV_1 has also been reported in patients with kidney failure on dialysis (9,10). Although a study among 29 kidney transplant recipients indicated that FEV_1 improves in the first months after successful transplantation, our study highlights that FEV_1 is still significantly lower in kidney transplant recipients compared with healthy controls, even at 1 year or longer after transplantation (30). Airflow limitation among kidney transplant recipients may thus partly be the result of previously acquired damage during the pretransplant period as a result of kidney failure and/or dialysis. Indeed, this notion is supported by our findings because kidney transplant recipients who underwent dialysis before transplantation were at higher risk of having airflow limitation (31–33).

Comorbidities after transplantation add up to previously acquired damage and may, therefore, contribute to airflow limitation. Indeed, diabetes, COPD, and sleep apnea syndrome were associated with airflow limitation in kidney transplant recipients, which is in line with results in other populations (6,12,14,34). Metabolic pathways related to insulin resistance causing subclinical weakness of respiratory muscles; intra-abdominal and intrathoracic fat, which may result in restriction of lung volume; defects in the bronchiolar surfactant layer; and low-grade chronic inflammation may explain the association with diabetes (6,7). Another comorbidity that may contribute to airflow limitation is (subclinical) pulmonary congestion as we found that a high NT-proBNP was associated with higher risk of airflow limitation. This is in line with studies in patients with heart failure that showed lower FEV_1, attributed to bronchial wall edema, and consequent reductions of lung compliance and obstruction (8).

Table 4. Associations of airflow limitation with health-related quality of life among kidney transplant recipients

		Health-Related Quality of Life			
		Physical Component Scale		Mental Component Scale	
Short Form-36	*N*	Difference (Standard Deviation), 95% Confidence Interval	*P* Value	Difference (Standard Deviation), 95% Confidence Interval	*P* Value
Crude	539	−0.13, –0.21 to –0.04	0.004	−0.11, –0.19 to –0.02	0.01
Model 1	539	−0.16, –0.24 to –0.08	<0.001	−0.12, –0.21 to –0.04	0.005
Model 2	525	−0.11, –0.19 to –0.03	0.006	−0.09, –0.18 to –0.01	0.04
Model 3	525	−0.11, –0.19 to –0.02	0.01	−0.08, –0.17 to 0.01	0.08

Standardized β-coefficients reflect the number of SDs difference in health-related quality of life if airflow limitation is present. Model 1 was adjusted for sex, age, and body mass index. Model 2 was model 1 additionally adjusted for diabetes, dialysis before transplantation, and $\log_2$ N-terminal prohormone of brain natriuretic peptide. Model 3 was model 2 additionally adjusted for history of smoking, mammalian target of rapamycin inhibitor use, sleep apnea syndrome , and chronic obstructive pulmonary disease.

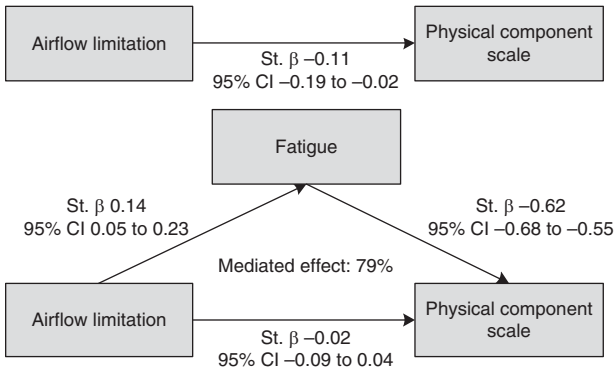

Figure 1. | Potential causal pathway of the mediated effect of fatigue on the association of airflow limitation with the physical component scale of health-related quality of life in kidney transplant recipients. Presented values are standardized β-coefficients (St. β-coefficients), which reflect the number of SDs change in fatigue or physical component scale scores if airflow limitation is present or the fatigue scores are higher with an SD, with 95% confidence intervals (95% CIs). Values were adjusted for sex, age, body mass index, dialysis before transplantation, $\log_2$ N-terminal prohormone of brain natriuretic peptide, history of smoking, mammalian target of rapamycin inhibitor use, sleep apnea syndrome, and chronic pulmonary obstructive disease. Mediation analyses were performed using 1000 bootstrapped samples of data from 511 kidney transplant recipients.

Kidney transplant recipients who use inhalation medication were at higher risk of airflow limitation, which was expected because patients using these drugs generally suffer from pulmonary diseases (*e.g.*, COPD or bronchial asthma). Additionally, our analyses showed that older kidney transplant recipients had lower risk of airflow limitation. This association is presumably caused by the clinician's judgment of transplant eligibility; whereas most young patients are considered eligible for kidney transplantation, transplantations among elderly patients may only be performed in those who are relatively fit and active compared with other patients of the same age. Elderly kidney transplant recipients may thus have relatively high FEV_1 compared with their age-matched healthy control counterparts. In addition, differences in comorbidities may partly explain the higher prevalence of airflow limitation among kidney transplant recipients compared with healthy controls. After all, comorbidities, including diabetes, heart failure, sleep apnea syndrome, and COPD, are prevalent among kidney transplant recipients, and they have all been linked to a decreased FEV_1 in other populations, as discussed.

Our study confirms that fatigue is a major clinical problem (2,21,35–37). Importantly, airflow limitation was independently associated with fatigue severity, suggesting that improving the FEV_1 might reduce fatigue in patients with airflow limitation. In addition, because a higher FEV_1 on a continuous scale was also independently associated with fatigue severity, even recipients without airflow limitation may benefit from FEV_1 improvement. Further analyses revealed that airflow limitation was independently associated with lower physical HRQoL. To investigate the potential causal pathway between airflow limitation and physical HRQoL, mediation analyses were performed. These analyses showed that the association between airflow limitation and physical HRQoL was strongly mediated by fatigue. This suggests that airflow limitation causes fatigue, which in turn, leads to a lower physical HRQoL.

One explanation of the found association with fatigue might be hypermetabolism; airflow limitation may cause increased energy expenditure for breathing. This notion is supported by studies that showed that patients suffering from severe COPD had higher resting metabolic rates compared with healthy controls (38,39). Potentially, the higher oxygen cost of breathing also plays a role (39). Similar mechanisms may also be present in kidney transplant recipients. FEV_1 can be improved by high-intensity aerobic exercise training and the use of bronchodilator medication (11,14,40–42). Airflow limitation is, therefore, a promising therapeutic target to alleviate fatigue and, consequently, improve physical HRQoL among kidney transplant recipients.

Strengths of this study are the large population size and the extensive available data regarding anthropometrics, medication use, and questionnaires. Consequently, we were able to adjust for many confounders and performed extensive sensitivity analyses. In addition, we were able to compare our findings in kidney transplant recipients with a large control group. A main limitation of our study is the lack of data on forced vital capacity to show whether the airflow limitation had a restrictive or obstructive etiology. Additionally, because of its observational design, we cannot draw conclusions regarding causality. Interventional studies are needed to assess the therapeutic potential of high-intensity aerobic exercise and/or inhalation medication to reduce airflow limitation, reduce fatigue, and improve physical HRQoL among kidney transplant recipients.

In conclusion, airflow limitation is common among kidney transplant recipients. Its occurrence is associated with more than twice the risk of severe fatigue, and it is independently associated with a lower physical HRQoL. Airflow limitation may, therefore, be an important and modifiable comorbidity in kidney transplant recipients. Mediation analyses suggest that airflow limitation causes fatigue, which in turn, decreases physical HRQoL. Future interventional studies are needed to investigate the therapeutic potential of high-intensity aerobic exercise and inhalation medication to alleviate fatigue and improve physical HRQoL of kidney transplant recipients.

Disclosures

C. Annema reports receiving research funding from Chiesi Pharmaceuticals BV and the Dutch Kidney Foundation and serving as a scientific advisor or member of the Dutch Transplant Society and the European Transplant Allied Health Professionals Committee of the European Society for Organ Transplantation. S.J.L. Bakker reports receiving research funding from Astellas Pharma and Chiesi and serving as a scientific advisor or member of the Dutch Health Council and the scientific board of the Dutch Kidney Foundation. S.P. Berger reports consultancy agreements with Novartis, receiving research funding from Chiesi and Novartis, receiving honoraria from Novartis, and serving as a scientific advisor or member of the advisory board of Novartis and the supervisory board of the Dutch Transplant Foundation. E. Corpeleijn is President of the Dutch Association for the Study of Obesity

(honorary). R.M. Douwes is supported by NWO/STW in a partnership program with DSM, Animal Nutrition and Health, The Netherlands (grant 14939). M.F. Eisenga reports consultancy agreements with Vifor Pharma, serving as a scientific advisor or member of the advisory board of Cablon Medical, and serving on the speakers bureau for Vifor Pharma. G. Navis reports serving as chair of the scientific board of the Dutch Kidney Foundation, a member of the Health Council of The Netherlands, and a member of the permanent advisory board of prevention of the Ministry of Health. All remaining authors have nothing to disclose.

Funding

This work was funded by Astellas grant TransplantLines Biobank and Cohort study.

Acknowledgments

Dr. S.J.L. Bakker designed the cohort; Dr. T.J. Knobbe, Dr. D. Kremer, Dr. M.F. Eisenga, Dr. A.W. Gomes-Neto, and Dr. S.J.L. Bakker acquired the data; Dr. T.J. Knobbe analyzed the data; Dr. C. Annema, Dr. S.J.L. Bakker, Dr. S.P. Berger, Dr. E. Corpeleijn, Dr. R.M. Douwes, Dr. M.F. Eisenga, Dr. C.T. Gan, Dr. A.W. Gomes-Neto, Dr. T.J. Knobbe, Dr. D. Kremer, Dr. G. Navis, and Dr. M. van Londen interpreted the data; Dr. T.J. Knobbe and Dr. D. Kremer wrote the manuscript; Dr. C. Annema, Dr. S.J.L. Bakker, Dr. S.P. Berger, Dr. E. Corpeleijn, Dr. R.M. Douwes, Dr. M.F. Eisenga, Dr. C.T. Gan, Dr. A.W. Gomes-Neto, Dr. G. Navis, and Dr. M. van Londen revised the manuscript; and Dr. S.J.L. Bakker adapted the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.06600521/-/DCSupplemental.

Supplemental Figure 1. Consort flow diagram.

Supplemental Table 1. Baseline characteristics of kidney transplant recipients in the study sample compared with the remaining patients in the parent cohort.

Supplemental Table 2. Fatigue and health-related quality of life assessments of kidney transplant recipients and healthy controls.

Supplemental Table 3. Mediated effect of fatigue on the association of airflow limitation with physical health-related quality of life in kidney transplant recipients.

Supplemental Table 4. Associations of airflow limitation (FEV_1<2.5th percentile) with fatigue among kidney transplant recipients.

Supplemental Table 5. Associations of airflow limitation (FEV_1<2.5th percentile) with health-related quality of life among kidney transplant recipients.

Supplemental Table 6. Associations of FEV_1 (continuous) with fatigue among kidney transplant recipients.

Supplemental Table 7. Associations of FEV_1 (continuous) with health-related quality of life among kidney transplant recipients.

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Received: May 10, 2021 **Accepted:** September 7, 2021

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Published online ahead of print. Publication date available at www.cjasn.org.

See related Patient Voice, "Understanding Fatigue with Kidney Disease: A Kidney Patient's Journey with Post-Transplant Fatigue" on pages 1611–1612.